British Heart Journal, 1977, **39**, 688–692

Massive digoxin ingestion
Report of a case and review of currently available therapies

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Recent reports of treatment of massive digoxin overdosage have emphasised the success of medical therapy. This report describes a fatal outcome to this problem despite aggressive medical management, including pervenous cardiac pacing and draws attention to deficiencies in current treatment of a serious problem.

Digoxin toxicity is not uncommon (Beller *et al.*, 1971; Boston Collaborative Drug Surveillance Program, 1972) and depends for successful treatment on its prompt recognition and withdrawal of glycoside therapy. This simple approach usually suffices and may be improved by routine monitoring of serum digoxin levels to detect occult toxicity.

Massive digoxin overdose is uncommon but much more dangerous: recent reports of successful management tend to obscure the high mortality rate, which may reach 20 per cent (Smith, 1973).

Case report

A 71-year-old man was admitted to the coronary care unit of the Royal Infirmary, Glasgow, some 14 hours after suicidal ingestion of 83 'Lanoxin' (Burroughs Wellcome) tablets of 0·25 mg strength. The number ingested was confirmed from the prescription date on the bottle.

The patient had been taking 0·25 mg digoxin per day together with a thiazide diuretic and potassium supplement for mild cardiac failure. He suffered from angina and prostatism and recently had been depressed.

On admission, the patient was semicomatose, hypotensive (90/60 mmHg), and vomiting repeatedly. He had no diarrhoea.

INVESTIGATIONS

An initial 12 lead electrocardiogram showed widespread ST depression and lead V6 detected a self-terminating run of ventricular tachycardia. Plasma electrolytes on admission were: Na 137, K 3·1, Cl 91, urea 7 mmol/l. Arterial blood gases were Po_2 58 per cent and Pco_2 31 per cent with *p*H 7·31. Magnesium and calcium levels were normal.

Haematology

Haemoglobin 18 g/dl; PCV 58 per cent, WBC $6{\cdot}4 \times 10^9$/l. Chest *x*-ray examination indicated a normal cardiac contour and possible pulmonary congestion.

Cardiac enzymes (on admission and 6 hours later) were subsequently reported to be normal.

Blood was drawn for digoxin radio-immunoassay. The level on admission was subsequently reported as 36·8 ng/ml (serum), and 45 minutes before death, the level was 56 ng/ml.

Six hours after admission, electrolyte parameters were Na 130, K 4·4, Cl 93, urea 7·5 mmol/l. Arterial blood *p*H was 7·31, Po_2 65 and Pco_2 was 41 (on 6 litres oxygen/minute).

PROGRESS AND MANAGEMENT

Cardiac rhythm was continuously monitored on a Hewlett-Packard video monitor with push-button recall and recording capacity.

Intravenous fluid replacement was started with normal saline and dextrose solutions with potassium supplements.

Vomiting ceased after intramuscular prochlorperazine.

In view of the hypotension, bladder catheterisation was performed to facilitate adequate monitoring of renal function. Urine output was initially low (urine osmolality 650 mosmol/kg), improved with

fluid replenishment and intravenous mannitol, but later declined again.

The patient's condition deteriorated and atropine-resistant bradyarrhythmia became more frequent. Under lignocaine cover (100 mg bolus and an infusion of 2 mg/min), a pacing catheter was passed from an antecubital vein to a pacing position on the floor of the right ventricle (threshold 0·4 volt).

Passage through the tricuspid valve induced ventricular fibrillation which was converted with three DC shocks of 50, 100, and, finally, 200 joules to a nodal bradycardia that permitted demand pacing at 100 beats/minute initially, subsequently reduced to a rate of 70/minute.

TREATMENT OF SUBSEQUENT RHYTHM DISORDERS

Sinus and nodal bradycardias were unresponsive to atropine (1·2 mg i.v.), and required pervenous pacing to maintain adequate organ haemoperfusion.

Runs of ventricular tachycardia were frequently self-terminating but where prolonged were treated with lignocaine bolus therapy (50, 100 mg i.v.). The prophylactic lignocaine infusion (2 mg/min) was maintained for 2 hours with no apparent reduction in the frequency of tachyarrhythmia and, therefore, was discontinued. To avoid lignocaine toxicity, boluses of practolol, procainamide and phenytoin were used in rotation to treat tachyarrhythmias causing haemodynamic deterioration. Procainamide was used sparingly in view of the patient's persistent hypotension.

Supraventricular tachycardias were treated with boluses of practolol and on two occasions, where they proved resistant to practolol, with procainamide boluses.

Some runs of supraventricular tachycardia changed to ventricular tachycardia and were aborted with lignocaine or procainamide boluses.

The practolol infusion (20 mg per 6 hours) was instituted to block digoxin-induced sympathetic stimulation and to raise the threshold for digoxin-induced ventricular fibrillation (Tse and Han, 1974).

Verapamil (10 mg i.v.) was given on two occasions: firstly, for a supraventricular tachycardia → ventricular tachycardia arrhythmia on the basis that this sequence might indicate a re-entry phenomenon—the tachycardia persisted until procainamide was given—and, secondly, for a run of atrial tachycardia with varying block—this arrhythmia changed to a rapid supraventricular tachycardia but then recurred.

A prolonged run of 2:1 atrial flutter was unresponsive to intravenous disopyramide, but converted with a procainamide/practolol bolus combination to a nodal bradycardia, permitting re-establishment of pacing rhythm.

TERMINAL EVENTS

By seven hours after admission, the ventricular complexes (both paced and unpaced) showed widening of the left bundle-branch block variety, the pulse volume was weak and urine output had fallen to 8 ml/hr.

Cardiac screening showed no change in pacemaker tip position but the pacing threshold had risen to 3·0 volts.

By this time, the patient had received, in divided doses, 820 mg lignocaine, 550 mg procainamide, 45 mg proctolol, 200 mg phenytoin, 20 mg verapamil, and 100 mg disopyramide.

Over the next two hours, the patient paced satisfactorily with no major rhythm upsets. The only therapy was a practolol infusion of 20 mg/6 hourly.

Nine hours after admission, an asystolic cardiac arrest occurred. External cardiac massage was initiated with no response. Cardiac pacing was unsuccessful despite re-manipulation and raising the pacing stimulus to 6 volts. Atrial pacing, similarly, was ineffectual.

Intravenous isoprenaline, 0·5 mg, induced coarse ventricular fibrillation but cardioversion at 30 joules produced a slow idioventricular rhythm that responded for a few beats to demand pacing, then reverted to ventricular fibrillation. Attempts to control the ventricular fibrillation by defibrillation, pacing, and phenytoin and procainamide boluses were unsuccessful and resuscitation was eventually abandoned.

Discussion

With the plethora of potentially useful (and hazardous) drugs currently available to treat massive digoxin overdosage, it is important to adopt a rational approach to this serious condition.

Firstly, it should be emphasised that digoxin-induced arrhythwias change frequently and spontaneously. Bigeminy does not necessarily portend ventricular tachycardia and the latter disorder may remit spontaneously. It follows that arrhythmias only require treatment if they cause haemodynamic deterioration. Attempts to use lignocaine or prophylatic practolol may be of little value and may in fact reduce the choice of therapy for the life-threatening arrhythmias.

Secondly, it is vital to reduce absorption, facilitate elimination of the drug and to deal with factors that potentiate the toxicity of digoxin. Gastric lavage should be performed when patients present shortly after ingestion or where vomiting has not

occurred. Purging, with close monitoring of plasma electrolytes, should also be considered, and might well have been beneficial in this case, in the light of the rise in serum digoxin levels after admission.

Maintenance of a good urinary output is mandatory as this is the major excretory route for digoxin. Mannitol is probably the safest diuretic, as electrolyte imbalance is least likely with osmotic diuretics. Maintenance and frequent monitoring of plasma electrolytes and *p*H are important as massive digoxin ingestion may produce hyperkalaemia caused by generalised cellular loss of potassium from blockage of the membrane sodium-potassium-pump, with subsequent cardiac arrest (Citrin *et al.*, 1972; Bismuth *et al.*, 1973). Induction of hyperkalaemia has been proposed as a therapeutic measure in digoxin overdosage as raised plasma potassium levels antagonise glycoside uptake at the sodium-potassium-pump site (Porter, 1974). This approach, however, may exacerbate bradycardia as potassium, while opposing digoxin-induced delay through the AV node, slows cardiac conduction by delaying transmission above and below the node (Dreifus *et al.*, 1974; Cohen *et al.*, 1975). Moreover, the beneficial effect of potassium is much reduced if given after glycoside fixation to cardiac tissue. This particular patient was hypokalaemic because of the central emetic effect of digoxin, and replenishment was undertaken cautiously as intermittent AV block was present.

Hypercalcaemia and hypomagnesaemia similarly potentiate digoxin toxicity (Nola *et al.*, 1970; Lee and Klaus, 1971; Seller, 1971 Beller *et al.*, 1973). Hypoxia was treated by controlled oxygen therapy (Harrison *et al.*, 1968; Beller and Smith, 1972; Beller *et al.*, 1973).

The *p*H was maintained by loss of gastric vomitus: acidosis appears to exert its potentiating effect through alterations in potassium (Bliss *et al.*, 1963).

Thirdly, attention is directed towards life-threatening arrhythmias. Sinus and nodal bradycardias may result from digoxin-induced vagal stimulation and will respond to atropine particularly shortly after digoxin ingestion. Resistance tends to appear (as here) probably because of binding of glycoside to cardiac tissue and direct effects of digoxin on sinus and AV nodal function. In these circumstances cardiac pacing is required.

Ventricular tachyarrhythmias are probably best treated in the first instance by lignocaine therapy as this drug is rapidly effective and, equally important, of short-lived effect. Hypotension is rarely a problem. A lignocaine bolus probably distributes itself into three compartments in man, with half-lives of 9, 40, and 120 minutes (Jewitt, 1975); the first compartment is of primary importance for antiarrhythmic action, but with repeated boluses other compartments may become saturated and toxic levels may be attained with the production of convulsions. Destruction is by hepatic microsomal enzymes.

A procainamide bolus may convert ventricular tachycardia but its use is limited by its slow rate of detoxication (10 to 15% of the bolus per hour) and by its tendency to cause hypotension. It does, however, have some anticholinergic activity and, unlike lignocaine, is effective in supraventricular tachycardia. Procainamide-induced asystole is relatively common in the presence of digoxin, and pacing may be life-saving.

Phenytoin is of similar efficacy to procainamide and has been recommended in digoxin overdosage on the grounds that it does not depress AV conduction (Mason *et al.*, 1971; Rumack *et al.*, 1974). However, the authors have observed that the combination of phenytoin and practolol induced complete heart block on two occasions in the same patient (with recurrent ventricular tachycardia secondary to ischaemic heart disease), and it may be that this potential benefit of phenytoin depends on the age and integrity of the conduction system. With a pervenous pacemaker *in situ*, this advantage is largely annulled.

Beta-adrenoreceptor blockade will abort digoxin-induced supraventricular tachycardia and, possibly, ventricular tachycardia (as apparently occurred here). There is evidence that digoxin poisoning can cause general sympathetic stimulation, both central and peripheral, and sympathetic stimulation lowers the threshold for digoxin-induced ventricular fibrillation (Tse and Han, 1974). On the basis of this evidence, practolol was used in bolus form to treat arrhythmia and as an infusion to counteract catecholamine discharge. Phenytoin is also said to oppose the central sympathetic effects of cardiac glycosides (Evans and Gillis, 1975).

The value of other antiarrhythmic drugs in digoxin poisoning is supported by experimental studies of their potential in opposing glycoside-induced ventricular fibrillation (Jewitt, 1975), but there is little experience of their efficacy in human overdosage. Verapamil, for example, was ineffective in this patient, as was disopyramide.

The ineffectiveness of verapamil merits further comment as this drug has been recommended in the treatment of atrial tachycardia with block on the basis that this rhythm is due to AV nodal re-entry (Storstein and Landmark, 1975). AV nodal action potentials are largely the result of the slow inward calcium current (which is not completely calcium-specific and may include a sodium component)

(Paes de Carvalho *et al.*, 1969), and verapamil antagonises the calcium influx through this channel. Theoretically, therefore, this drug should offer distinct advantages in the treatment of atrial tachycardia (and this has been shown to be so by Storstein and Landmark, 1975; Spurrell *et al.*, 1974) and also of digoxin intoxication as digoxin appears to augment calcium influx by increasing intracellular sodium. The lack of effect in this patient may indicate that the toxic effects of digoxin were too far advanced for verapamil at the chosen therapeutic dose to reverse the rhythm abnormalities.

Cardioversion should be a last resort: digoxin excess lowers the size of shock required and tends to produce intractable or recurrent tachyarrhythmias (Ten Eick *et al.*, 1967; Peleška, 1963; Lown *et al.*, 1965).

The inexorable decline in response to pacing is probably a measure of increasing glycoside fixation to cardiac tissue, as is the resistance of bradycardias to atropine.

Digoxin appears to exert its effects on cardiac tissue by blocking the membrane-located sodium-potassium pump: the consequent rise in intracellular sodium accelerates transfer of calcium into cells in exchange for sodium; the rise in internal calcium augments myocardial contractility by activating troponin.

Toxicity is primarily a pharmacological extension of this action of digoxin with ionic imbalance predisposing to ectopic activity re-entry rhythms, and conduction delay or enhancement. At high glycoside levels, calcium accumulates at cell nexuses producing electrical uncoupling and failure of impulse transmission (Weingart, 1975). This was the probable terminal sequence in this patient. The plasma digoxin levels recorded here are possibly the highest recorded in a human being.

Currently, the major problem in reversing digoxin toxicity is the lack of a generally available method of removing glycoside from the bloodstream. Haemodialysis and charcoal perfusion are valueless.

Recently, Smith *et al.* (1976) have shown the effectiveness and safety of an infusion of Fab fragments purified from digoxin antibodies in leaching out digoxin from tissues in animals and in a human patient; the fragments attach to glycoside and are sufficiently small to permit glomerular excretion. This promises to be a major breakthrough in the treatment of a difficult problem.

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